Remarks

Claims 1 and 2 are pending. In view of the above amendment and the following remarks, reconsideration and allowance of the application are respectfully requested. The specification is amended to insert text otherwise found only in the claims. No new matter is believed added.

Objection to the Specification

In response to this objection, applicants have amended the specification to add language corresponding to claim 1, particularly "diabetic ischemia of a foot." The patent law allows applicant to amend the specification to insert language found only in the specification. Furthermore, the full text of the insertion is supported for the reasons "differentially" is supported in the application. Thus, this is believed to overcome this objection, and its withdrawal is respectfully requested.

Claim Rejections – 35 USC § 112

The present rejection is an exact duplicate of the rejection stated in the April 6, 2006 Office Action. Applicants responded to this rejection with detailed arguments in the response of July 10, 2006.

The Examiner notes in response to applicants' prior remarks that it is not clear that this differentially removing of high molecular weight proteins is only based on pore size of a filter, since other methods of removing high molecular weight protein may be used. The current rejection also states the following: "It is noted that Applicant sets forth that 'several plasma differential separation techniques' may remove high molecular

weight protein in the specification. Furthermore, applicant does not give specific information on the filter pore sizes, but rather only gives examples of filters by trade names (see paragraph [0032]). Therefore, it does not preclude one from having to do undue experimentation to determine what constitutes how to 'differentially' remove protein from the blood.

Applicants note that this is an entirely new rejection, not based on new matter as the previous rejection was. In fact this seems to be stated as an enablement.

In response to the substance of this new rejection, the fact that specific commercial filters are mentioned provides specific examples of the pore sizes that can be used in the method. The Examiner provides no basis to assert that this information not sufficient to preclude undue experimentation. In fact, the information provided by reference to these commercial products, well known and well characterized in both the commercial and scientific literature, would be expected to negate the need for undue experimentation. This seems to be a common sense perspective, and the Examiner has not provided any reason not to rely on this when analyzing this matter for enablement.

Furthermore, the law of section 112 does not require that applicants' specification "preclude" undue experimentation as recited in the Examiners comments. Rather the rule is that applicants' specification must provide sufficient information such that undue experimentation is not required. By teaching differential separation based on size and by providing specific examples of filters that can be used, no experimentation is needed to practice the method. Thus, the current rejection is not founded on any substantial factual or legal basis. Thus, withdrawal of this rejection is believed to be merited and is respectfully requested.

Rejection under 35 U.S.C. § 103

A. Claims 1 and 2 are rejected as allegedly obvious over Georgadze et al. in view of Malchesky et al.

With respect to the Georgadze et al. the examiner points out that this document describes plasmapheresis treatment which may be used for the treatment of ischemia in the lower extremities of diabetics. In the view of the examiner the reference discloses that the plasmapheresis corrects the biochemical and coagulation parameters of the blood and thereby preserves the extremity from amputation in most patients.

The examiner concludes that with respect to the treatment of the foot it would have been obvious for persons skilled in the art based on the teaching of Georgadze et al. to use plasmapheresis as treatment for persons diagnosed with diabetic ischemia of the foot since the foot is obviously a lower extremity. According to the Examiner, such treatment would be beneficial to preserve the foot from amputation. Regarding the specific removal of high molecular weight protein, the examiner asserts it would have been within ordinary skill to choose a method to remove proteins of any desired size, such as high molecular weight proteins, using the method of Georgadze et al.

Claim 1 recites that the claimed method of treatment differentially removes high molecular weight proteins from the blood. The recitation of this feature illustrates a non-obvious distinction over the cited Georgadze et al. reference.

Georgadze et al. does not suggest the selective removal of large molecular weight proteins in that it fails to mention this approach and it fails to provide any motivation for selective removal. Furthermore, it can be concluded from the first page 2nd paragraph that the centrifugation plasmapheresis technique described in the Georgadze et al.

document leads to the non-selective elimination of numerous types of blood components that can contribute to diabetic ischemia. This procedure is, by its very nature, non-selective. Thus, not only is there no explicit suggestion, there is no implicit suggestion in Georgadze et al. to selectively remove large molecular weight proteins. In contrast, the treatment according to the invention selectively removes high molecular weight proteins and preferably low density lipoprotein, cholesterol, alpha-2-macroglobulin and similar high molecular weight proteins.

Furthermore the reference teaches that a medicament Rheopolyglukin was used as an infusion substance (see page 2, 2nd paragraph of English translation). Such a medicament is not used in the treatment according to the present invention. While this component of the Georgadze et al. method is not stated in the reference to be required for success, it is unpredictable that the method would work without this component. Thus, because the reference used Rheopolyglukin, and suggests its future use (see page 5, item 2 of the Conclusions), the reference does not suggest a method in which it is not used. Since the method of the invention does not use this component, the invention is not suggested by the reference. The current Office Action does not explicitly address this argument previously made by applicants. In fact, applicants made this argument first in their response file April 18, 2005, and in each subsequent response have asked for its consideration. Since it is relevant to the issue of obviousness, the Examiner should address it explicitly.

The present invention uses method steps that differ from and are not suggested by Georgadze et al., namely, that specific high molecular weight proteins are removed from the blood of the patient. After that, the blood is reinfused into the patient and thereby the

diabetic ischemia of the foot is treated. Georgadze et al. has the disadvantage of being less selective than the present invention. As explained above the treatment according to the invention is very selective compared to the gravitational plasmapheresis treatment according to the Georgadze et al. reference.

The conclusion of the in the office action that it was obvious for persons skilled in the art based on the teaching of Georgadze et al. to use plasmapheresis as treatment for persons diagnosed with diabetic ischemia of the foot is wrong for the present claim because Georgadze et al. discloses a totally different plasmapheresis procedure compared to the claimed invention. This procedure discloses a technique in which toxic substances are removed from the blood, but not by the selective removal of large molecular weight protein components of the blood. Since there is no suggestion in Georgadze et al. of any advantage to the selective removal of high molecular weight protein, there is no motivation in this reference to do so or to combine its teaching with art that does. Furthermore, there is no motivation in Malchesky et al. to apply its teaching to the method of Georgadze et al. or in the context of diabetic ischemia of a foot. There is also no motivation in Georgadze et al. to apply the teaching of Malchesky et al. to its method or in its context of use. Neither reference is directed to the science or practice of hemorheology. Georgadze et al. is focused on purification of the blood, not on the improvement of the general state of blood fluidity (hemorheology), which is what the present invention is concerned with. Likewise, Malchesky et al. is directed to the treatment of diseases associated with specific blood solutes, not the general state of blood fluidity. In fact, Malchesky specifically mentions diabetic hypertriglyceridemia, because it is associated with elevated triglycerides (a specific blood solute), but does not mention

diabetic ischemia because it would not have been apparent that the methods disclosed would treat diabetic ischemia. Thus, there is no suggestion in Malchesky et al. that the method taught therein would have any relevance to diabetic ischemia. Since there is no suggestion in Georgadze et al. of the relevance of hemorheology in the treatment of diabetic ischemia, and since there is no suggestion in Malchesky of either 1) any value to changing blood fluidity or 2) applicability to diabetic ischemia of a foot, there is no motivation to use the technique of Malchesky et al. to modify the method of Georgadze et al. to treat diabetic ischemia.

Since neither reference discloses or suggests any value for changing blood fluidity (hemorheology), neither suggests the aspect of the claimed invention that is missing from the other reference. Because the references taken alone or together do not suggest the application of size-based selective removal of high molecular weight proteins from the blood to treat diabetic ischemia of a foot, the invention of claims 1 and 2 is not obvious over the art.

B. Claims 1 and 2 are rejected as allegedly obvious over Seidel et al. (4,923,439) in view of Georgadze et al.

Seidel et al. relates to a process for the selective extracorporeal precipitation of low density lipoproteins from whole serum or plasma. The reference further describes an apparatus for the continuous therapeutic practice of such a process. Furthermore, the references are silent on describing a method for treating ischemia of the foot. Therefore, for reasons very similar to those recited for non-combination with Malchesky et al., the person skilled in the art would not combine the document of Georgadze et al. and the document of Seidel et al. More specifically, the molecules being removed by Seidel et al.

are very different from the high molecular weight proteins removed in the present method. Thus, differential removal of high molecular weight proteins is not taught. Georgadze et al. also do not teach this aspect of the claims. Thus, the combination does not teach differential removal of high molecular weight proteins as claimed.

To further assist the Examiner in recognizing the differences among the claimed invention and the cited art, applicants provide comparison tables (Exhibits A and B) that show additional differences between the claimed method and the methods of the art.

Secondary Considerations

The letter of Dr. Schmid-Schönbein submitted with applicants response of December 12, 2005, explains the concept of hemorheology and notes the failure of the prior art to suggest its application for the treatment of diseases such as diabetic ischemia of a foot. The letter of Dr. Schmid-Schönbein also acknowledges the significant contribution of the present invention to the art of treating diabetes. It is noted that the Examiner has not addressed the content of this letter. Since it is an important consideration for an obviousness analysis, it is due specific consideration, which has not yet been provided by the Examiner. Thus, it is respectfully requested that any subsequent rejection specifically take into consideration this evidence of non-obviousness.

Furthermore, the fact that others have adopted the method of the claims means that the present invention satisfies a previously unsatisfied need. See Exhibit A: Richter et al., Extracorporeal fibrinogen adsorption--efficacy, selectivity and safety in healthy subjects and patients with foot ulcers, Transfus Apher Sd. 2002 Feb;26(1): 15-27; and Exhibit B: Klingel et al., Rheopheresis in patients with ischemic diabetic foot syndrome: results of an open label prospective pilot trial, Ther Apher Dial. 2003 Aug;7(4):444-55,

submitted with applicants' December 12, 2005 response. It is noted that the Examiner has not addressed the content of these publications. Since this evidence is an important consideration for an obviousness analysis, it is due specific consideration, which has not yet been provided by the Examiner. Thus, it is respectfully requested that any subsequent rejection specifically take into consideration this evidence of long felt need and adoption by the relevant art of the claimed method.

In view of the above remarks and previous remarks and evidence, reconsideration and allowance of the pending application are respectfully requested. The Examiner is invited to contact the undersigned counsel by telephone if such contact would expedite prosecution.

No additional fee is believed due. However, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

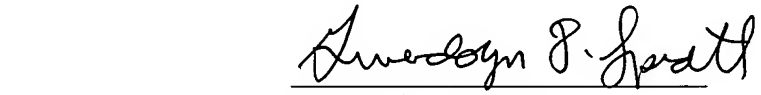

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EXHIBIT A

Author	Malchesky et al.	Borberg et al. (present app.)
Target (Indication)	Treatment of cryoglobulinemia, myeloma or immune complexes	Treatment of diseases of the microcirculation such as diabetic foot
Procedure	Remover of cryoprecipitates or cryoglobulins	Extracorporeal haemorheotherapy
Technique	Cooling of separated plasma with subsequent heating or adding complexing agents to the plasma with subsequent removal	On-line differential filtration from plasma without cooling or adding complexing agents
Application of filters	Restricted to the selective removal of cryoprecipitates or complexed gels	Elimination of high molecular weight proteins from plasma
Rheological effects	Neither investigated nor mentioned nor applied for	Investigated
Diabetic ischemic foot	Not taken into consideration, not investigated,	Investigated
Final judgement	No widespread application	World wide application since first patent application; Corresponding US patent for treatment of other diseases (6,627,151)

EXHIBIT B

Author	Seidel et al.	Borberg et al. (present app.)
Target (Indication)	Treatment of early atherosclerosis	Treatment of diseases of the microcirculation such as diabetic foot
Procedure	Selective removal of low density lipoprotein only	Extracorporeal haemorheotherapy
Technique	Precipitation in combination with another 4 different procedural steps	On-line differential filtration from plasma without cooling or adding complexing agents
Application of filters	Removal of precipitates	Elimination of high molecular weight proteins from plasma
Rheological effects	Neither investigated nor mentioned	Investigated
Diabetic ischemic foot	Not taken into consideration, not investigated,	Investigated
Final judgement	No widespread application (not practical, expensive)	World wide application since first patent application; Easy to perform and inexpensive; Corresponding US patent for treatment of other diseases (6,627,151)